

University of Dundee

## Thyroid function in preterm infants and neurodevelopment at 2 years

Williams, Fiona L. R.; Lindgren, Alice; Watson, Jennifer; Boelen, Anita; Cheetham, Tim

*Published in:*  
Archives of Disease in Childhood. Fetal and Neonatal edition

*DOI:*  
[10.1136/archdischild-2018-316742](https://doi.org/10.1136/archdischild-2018-316742)

*Publication date:*  
2020

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*  
Williams, F. L. R., Lindgren, A., Watson, J., Boelen, A., & Cheetham, T. (2020). Thyroid function in preterm infants and neurodevelopment at 2 years. *Archives of Disease in Childhood. Fetal and Neonatal edition*, 105(5), 504-509. <https://doi.org/10.1136/archdischild-2018-316742>

### General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

## **METHODS**

### **Assay measurement information**

All assays were measured according to the manufacturer's protocol: TSH by an immunometric assay (Brahms, Thermo scientific, Henningsdorf, Germany, intra-assay variation 6.2%, inter-assay variation 12.9%) and total T4 by fluoro-immunoassay (AutoDelfia, Perkin Elmer, Waltham, MA, intra-assay variation 8.2%, inter-assay variation 10.7%).

TBG (years 2010 and 2011) was measured using a radioimmunoassay kit (RIA; Eiken, Japan, intra-assay variation 12.6%, inter-assay variation 8.0%). This TBG kit is intended for measurement in serum and was modified for measurement in dried bloodspots.<sup>17</sup> This assay was replaced after extensive validation by an ELISA (Monobind, USA, intra-assay variation 9.7%, inter-assay variation 12.5%) on January 1<sup>st</sup> 2012.

## **RESULTS**

### **Clinical characteristics**

During the neonatal period, 11 infants who had TSH levels  $\geq 6\text{mU/L}$  were treated with Levothyroxine (11/69) and received a 'working/potential diagnosis' of hypothyroidism (treatment with Levothyroxine had no statistical impact on any domain of neurodevelopmental outcome). One additional infant was treated with Levothyroxine for hypopituitarism and two additional infants were given the 'diagnosis' of hypothyroidism but not treated. At two years of age, 7 of the 11 infants who were treated neonatally remained on treatment. A further 6 infants, who were not identified through the trial to have thyroid dysfunction, were reported by their parents to be receiving Levothyroxine for hypothyroidism.

### **Infants with elevated TSH levels**

The characteristics of the six infants (4.9 per 1000, 6/1222) with elevated TSH levels noted for the first time when they were measured at the equivalent of 34 weeks' gestation were:

- mean gestation at birth was 27 weeks (range 24-30 weeks)
- they were therefore between 4-10 weeks' chronological age at the equivalent of 34 weeks' gestation
- three infants were male and three were female
- (on postnatal day 14) two infants were receiving level 1 care, two infants level 2 care, and two infants level 3 care.

We do not know whether these were isolated raised levels as no further follow-up of thyroid function was recorded although none received Levothyroxine either during the neonatal period or at 2 years of age. It is of note that many preterm babies with subtle thyroid dysfunction do not have classical congenital hypothyroidism due to dysgenesis.

### **Infants treated with Levothyroxine reported by their parents at follow up**

Six infants were not identified through the trial to have thyroid dysfunction but were reported by their parents to be receiving Levothyroxine for hypothyroidism. These 6 infants all had normal TSH levels recorded on study bloods: three infants were classified from study bloods as hypothyroxinaemic and one infant was euthyroid; four infants were male, and the mean gestation was  $25.2 \pm 2.6$  weeks. Thus at two years of age, 13 infants were receiving Levothyroxine.

**SUPPLEMENTARY TABLE 1:** Adjusted<sup>1</sup> linear regression models of T4/TBG ratio taken over at least two study bloods and the Bayley-III main and subtest domains

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Cognitive Score</b>						
Consistent bottom decile	2	-12.6	-1.158	0.247	-33.9	8.8
Mixed deciles	257	0.3	0.273	0.785	-1.9	2.5
Never in bottom decile	731	reference				
<b>Motor Composite Score</b>						
Consistent bottom decile	2	-34.5	-3.284	0.001	-55.1	-13.9
Mixed deciles	256	<0.1*	-0.064	0.949	-2.2	2.1
Never in bottom decile	731	reference				
<b>Language Composite Score</b>						
Consistent bottom decile	2	-13.1	-1.075	0.283	-37.2	10.9
Mixed deciles	256	0.5	0.416	0.677	-2.0	3.1
Never in bottom decile	730	reference				
<b>Receptive Language Subtest</b>						
Consistent bottom decile	2	-1.8	-0.806	0.420	-6.1	2.5
Mixed deciles	256	<0.1	0.377	0.706	-0.4	0.5
Never in bottom decile	730	reference				
<b>Expressive Language Subtest</b>						
Consistent bottom decile	2	-2.8	-1.238	0.216	-7.2	1.6
Mixed deciles	256	<0.1	0.329	0.742	-0.4	0.5
Never in bottom decile	729	reference				
<b>Fine Motor Subtest</b>						
Consistent bottom decile	1	-8.2	-2.838	0.005	-13.9	-2.5
Mixed deciles	256	0.3	1.150	0.250	-0.2	0.7
Never in bottom decile	731	reference				
<b>Gross Motor Subtest</b>						
Consistent bottom decile	2	-3.4	-1.806	0.071	-7.1	0.3
Mixed deciles	257	-0.3	-1.408	0.159	-0.7	0.1
Never in bottom decile	730	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day 14, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor and hospital of birth

\*Actual figure is -0.70

**SUPPLEMENTARY TABLE 2:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III Cognitive scores

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Cognitive Score Day 7</b>						
Top decile TSH <sup>2</sup>	184	-1.2	-0.904	0.366	-3.7	1.4
Remainder deciles TSH	755	reference				
Bottom decile TBG	83	-0.2	-0.086	0.932	-3.6	3.3
Remainder deciles TBG	856	reference				
Bottom decile T4/TBG ratio	88	2.0	1.166	0.244	-1.4	5.4
Remainder deciles T4/TBG ratio	851	reference				
Bottom decile T4	93	-1.3	-0.768	0.443	-4.7	2.1
Remainder deciles T4	854	reference				
<b>Cognitive Score Day 14</b>						
Top decile TSH	182	-2.8	-2.175	0.030	-5.4	-0.3
Remainder deciles TSH	770	reference				
Bottom decile TBG	86	-2.6	-1.499	0.134	-6.0	0.8
Remainder deciles TBG	866	reference				
Bottom decile T4/TBG ratio	91	0.6	0.351	0.726	-2.8	4.0
Remainder deciles T4/TBG ratio	861	reference				
Bottom decile T4	86	-3.5	-1.995	0.046	-6.9	-0.1
Remainder deciles T4	869	reference				
<b>Cognitive Score Day 28</b>						
Top decile TSH	131	-1.6	-1.071	0.285	-4.4	1.3
Remainder deciles TSH	780	reference				
Bottom decile TBG	88	-0.4	-0.226	0.821	-3.8	3.0
Remainder deciles TBG	824	reference				
Bottom decile T4/TBG ratio	81	-2.4	-1.327	0.185	-5.9	1.1
Remainder deciles T4/TBG ratio	831	reference				
Bottom decile T4	79	-0.7	-0.376	0.707	-4.3	2.9
Remainder deciles T4	834	reference				
<b>Cognitive Score 34 weeks'</b>						
Top decile TSH	270	-1.4	-1.256	0.210	-3.6	0.8
Remainder deciles TSH	593	reference				
Bottom decile TBG	87	-0.9	-0.543	0.587	-4.4	2.5
Remainder deciles TBG	776	reference				
Bottom decile T4/TBG ratio	74	1.4	0.754	0.451	-2.3	5.2
Remainder deciles T4/TBG ratio	789	reference				
Bottom decile T4	80	-0.6	-0.293	0.769	-4.2	3.1
Remainder deciles T4	783	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth, and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

<sup>2</sup>the top decile for TSH is actually the top 9-14% dependent on day of test as the TSH kit only provided integer results

**SUPPLEMENTARY TABLE 3:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III Motor Composite scores

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Motor Composite Score Day 7</b>						
Top decile TSH <sup>2</sup>	184	-1.3	-1.052	0.293	-3.8	1.2
Remainder deciles TSH	754	reference				
Bottom decile TBG	83	-0.2	-0.141	0.888	-3.6	3.1
Remainder deciles TBG	855	reference				
Bottom decile T4/TBG ratio	87	1.9	1.150	0.251	-1.4	5.2
Remainder deciles T4/TBG ratio	851	reference				
Bottom decile T4	93	-0.1	-0.075	0.940	-3.4	3.2
Remainder deciles T4	853	reference				
<b>Motor Composite Score Day 14</b>						
Top decile TSH	182	-2.4	-1.873	0.061	-4.8	0.1
Remainder deciles TSH	769	reference				
Bottom decile TBG	86	-0.2	-0.122	0.903	-3.5	3.1
Remainder deciles TBG	865	reference				
Bottom decile T4/TBG ratio	90	-1.3	-0.750	0.453	-4.5	2.0
Remainder deciles T4/TBG ratio	861	reference				
Bottom decile T4	86	-3.4	-1.974	0.049	-6.7	<-0.1
Remainder deciles T4	868	reference				
<b>Motor Composite Score Day 28</b>						
Top decile TSH	131	-0.8	-0.553	0.580	-3.5	2.0
Remainder deciles TSH	779	reference				
Bottom decile TBG	88	-0.3	-0.148	0.882	-3.5	3.0
Remainder deciles TBG	823	reference				
Bottom decile T4/TBG ratio	80	-3.0	-1.757	0.079	-6.4	0.4
Remainder deciles T4/TBG ratio	831	reference				
Bottom decile T4	79	-0.9	-0.490	0.625	-4.4	2.6
Remainder deciles T4	833	reference				
<b>Motor Composite Score 34 weeks'</b>						
Top decile TSH	270	-1.0	-0.915	0.360	-3.2	1.2
Remainder deciles TSH	592	reference				
Bottom decile TBG	87	<0.1	0.043	0.966	-3.2	3.4
Remainder deciles TBG	775	reference				
Bottom decile T4/TBG ratio	74	0.6	0.310	0.757	-3.0	4.2
Remainder deciles T4/TBG ratio	788	reference				
Bottom decile T4	80	-1.5	-0.820	0.412	-5.0	2.1
Remainder deciles T4	781	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth, and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

<sup>2</sup>the top decile for TSH is actually the top 9-14% dependent on day of test as the TSH kit only provided integer results

**SUPPLEMENTARY TABLE 4:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III Language Composite scores

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Language Composite Score Day 7</b>						
Top decile TSH <sup>2</sup>	184	-2.4	-1.663	0.097	-5.3	0.4
Remainder deciles TSH	753	reference				
Bottom decile TBG	83	0.1	0.071	0.943	-3.8	4.1
Remainder deciles TBG	854	reference				
Bottom decile T4/TBG ratio	87	2.1	1.064	0.287	-1.8	5.9
Remainder deciles T4/TBG ratio	850	reference				
Bottom decile T4	92	-1.6	-0.823	0.410	-5.4	2.2
Remainder deciles T4	853	reference				
<b>Language Composite Score Day 14</b>						
Top decile TSH	182	-2.8	-1.904	0.057	-5.6	0.1
Remainder deciles TSH	769	reference				
Bottom decile TBG	86	-2.7	-1.368	0.172	-6.5	1.2
Remainder deciles TBG	865	reference				
Bottom decile T4/TBG ratio	91	0.1	0.032	0.974	-3.7	3.8
Remainder deciles T4/TBG ratio	860	reference				
Bottom decile T4	86	-3.1	-1.591	0.112	-7.0	0.7
Remainder deciles T4	868	reference				
<b>Language Composite Score Day 28</b>						
Top decile TSH	131	-2.1	-1.254	0.210	-5.3	1.2
Remainder deciles TSH	778	reference				
Bottom decile TBG	88	0.2	0.082	0.935	-3.7	4.0
Remainder deciles TBG	822	reference				
Bottom decile T4/TBG ratio	81	-3.1	-1.548	0.122	-7.1	0.8
Remainder deciles T4/TBG ratio	829	reference				
Bottom decile T4	79	-0.6	-0.279	0.780	-4.6	3.5
Remainder deciles T4	832	reference				
<b>Language Composite Score 34 weeks'</b>						
Top decile TSH	269	-1.1	-0.885	0.376	-3.6	1.4
Remainder deciles TSH	592	reference				
Bottom decile TBG	87	-0.5	-0.259	0.795	-4.3	3.3
Remainder deciles TBG	774	reference				
Bottom decile T4/TBG ratio	74	1.1	0.508	0.611	-3.0	5.1
Remainder deciles T4/TBG ratio	787	reference				
Bottom decile T4	80	1.5	0.738	0.461	-2.5	5.6
Remainder deciles T4	781	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth, and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

<sup>2</sup>the top decile for TSH is actually the top 9-14% dependent on day of test as the TSH kit only provided integer results

**SUPPLEMENTARY TABLE 5:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III Receptive language subtest scores

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Receptive Language Score Day 7</b>						
Top decile TSH <sup>2</sup>	184	-0.2	-0.918	0.359	-0.8	0.3
Remainder deciles TSH	753	reference				
Bottom decile TBG	83	<0.1	0.030	0.976	-0.7	0.7
Remainder deciles TBG	854	reference				
Bottom decile T4/TBG ratio	87	0.4	1.006	0.315	-0.3	1.0
Remainder deciles T4/TBG ratio	850	reference				
Bottom decile T4	92	-0.4	-1.069	0.285	-1.1	0.3
Remainder deciles T4	853	reference				
<b>Receptive Language Score Day 14</b>						
Top decile TSH	182	-0.4	-1.390	0.165	-0.9	0.2
Remainder deciles TSH	769	reference				
Bottom decile TBG	86	-0.5	-1.449	0.148	-1.2	0.2
Remainder deciles TBG	865	reference				
Bottom decile T4/TBG ratio	91	<0.1	-0.140	0.889	-0.7	0.6
Remainder deciles T4/TBG ratio	860	reference				
Bottom decile T4	86	-0.7	-1.901	0.058	-1.4	<0.1
Remainder deciles T4	868	reference				
<b>Receptive Language Score Day 28</b>						
Top decile TSH	131	-0.3	-1.108	0.268	-0.9	0.3
Remainder deciles TSH	778	reference				
Bottom decile TBG	88	<0.1	-0.111	0.912	-0.8	0.7
Remainder deciles TBG	822	reference				
Bottom decile T4/TBG ratio	81	-0.5	-1.342	0.180	-1.2	0.2
Remainder deciles T4/TBG ratio	829	reference				
Bottom decile T4	79	-0.4	-0.952	0.342	-1.1	0.4
Remainder deciles T4	832	reference				
<b>Receptive Language Score 34 weeks'</b>						
Top decile TSH	269	-0.2	-0.661	0.509	-0.6	0.3
Remainder deciles TSH	592	reference				
Bottom decile TBG	87	-0.3	-0.791	0.429	-1.0	0.4
Remainder deciles TBG	774	reference				
Bottom decile T4/TBG ratio	74	0.2	0.518	0.604	-0.6	0.9
Remainder deciles T4/TBG ratio	787	reference				
Bottom decile T4	80	0.1	0.238	0.812	-0.6	0.8
Remainder deciles T4	781	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

<sup>2</sup>the top decile for TSH is actually the top 9-14% dependent on day of test as the TSH kit only provided integer results

**SUPPLEMENTARY TABLE 6:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III Expressive language subtest scores

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Expressive Language Score Day 7</b>						
Top decile TSH <sup>2</sup>	184	-0.6	-2.214	0.027	-1.1	<-0.1
Remainder deciles TSH	752	reference				
Bottom decile TBG	83	<0.1	0.049	0.961	-0.7	0.7
Remainder deciles TBG	853	reference				
Bottom decile T4/TBG ratio	87	0.3	0.923	0.356	-0.4	1.0
Remainder deciles T4/TBG ratio	849	reference				
Bottom decile T4	92	-0.2	-0.630	0.529	-0.9	0.5
Remainder deciles T4	852	reference				
<b>Expressive Language Score Day 14</b>						
Top decile TSH	182	-0.6	-2.223	0.026	-1.1	<-0.1
Remainder deciles TSH	768	reference				
Bottom decile TBG	86	-0.4	-1.164	0.245	-1.1	-0.3
Remainder deciles TBG	864	reference				
Bottom decile T4/TBG ratio	91	<0.1	0.153	0.878	-0.6	0.7
Remainder deciles T4/TBG ratio	859	reference				
Bottom decile T4	86	-0.4	-1.119	0.263	-1.1	0.3
Remainder deciles T4	867	reference				
<b>Expressive Language Score Day 28</b>						
Top decile TSH	131	-0.4	-1.319	0.188	-1.0	0.2
Remainder deciles TSH	777	reference				
Bottom decile TBG	88	0.1	0.263	0.793	-0.6	0.8
Remainder deciles TBG	821	reference				
Bottom decile T4/TBG ratio	81	-0.6	-1.592	0.112	-1.3	0.1
Remainder deciles T4/TBG ratio	828	reference				
Bottom decile T4	79	0.2	0.400	0.690	-0.6	0.9
Remainder deciles T4	831	reference				
<b>Expressive Language Score 34 weeks'</b>						
Top decile TSH	269	-0.3	-1.116	0.265	-0.7	0.2
Remainder deciles TSH	591	reference				
Bottom decile TBG	87	<0.1	0.238	0.812	-0.6	0.8
Remainder deciles TBG	773	reference				
Bottom decile T4/TBG ratio	74	0.2	0.441	0.659	-0.6	0.9
Remainder deciles T4/TBG ratio	786	reference				
Bottom decile T4	80	0.4	1.065	0.287	-0.3	1.1
Remainder deciles T4	780	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

<sup>2</sup>the top decile for TSH is actually the top 9-14% dependent on day of test as the TSH kit only provided integer results



**SUPPLEMENTARY TABLE 7:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III Fine Motor subtest scores

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Fine motor Score Day 7</b>						
Top decile TSH <sup>2</sup>	184	-0.3	-1.006	0.315	-0.7	0.2
Remainder deciles TSH	753	reference				
Bottom decile TBG	83	-0.2	-0.466	0.641	-0.8	0.5
Remainder deciles TBG	854	reference				
Bottom decile T4/TBG ratio	86	0.7	1.947	0.052	<-0.1	1.3
Remainder deciles T4/TBG ratio	851	reference				
Bottom decile T4	93	<0.01	0.008	0.993	-0.7	0.7
Remainder deciles T4	852	reference				
<b>Fine motor Score Day 14</b>						
Top decile TSH	182	-0.6	-2.321	0.021	-1.1	<-0.1
Remainder deciles TSH	768	reference				
Bottom decile TBG	86	-0.4	-1.267	0.205	-1.1	0.2
Remainder deciles TBG	864	reference				
Bottom decile T4/TBG ratio	89	<0.1	0.256	0.798	-0.6	0.7
Remainder deciles T4/TBG ratio	861	reference				
Bottom decile T4	86	-0.5	-1.515	0.130	-1.2	0.2
Remainder deciles T4	867	reference				
<b>Fine motor Score Day 28</b>						
Top decile TSH	131	-0.2	-0.851	0.395	-0.8	0.3
Remainder deciles TSH	779	reference				
Bottom decile TBG	88	-0.2	-0.600	0.549	-0.8	0.5
Remainder deciles TBG	823	reference				
Bottom decile T4/TBG ratio	80	-0.8	-2.294	0.022	-1.5	-0.1
Remainder deciles T4/TBG ratio	831	reference				
Bottom decile T4	79	0.2	0.426	0.671	-0.5	0.8
Remainder deciles T4	833	reference				
<b>Fine motor Score 34 weeks'</b>						
Top decile TSH	270	-0.4	-1.899	0.058	-0.8	<0.1
Remainder deciles TSH	591	reference				
Bottom decile TBG	87	0.2	0.547	0.584	-0.5	0.8
Remainder deciles TBG	774	reference				
Bottom decile T4/TBG ratio	73	0.4	1.231	0.219	-0.3	1.2
Remainder deciles T4/TBG ratio	788	reference				
Bottom decile T4	80	-0.2	-0.626	0.531	-0.9	0.5
Remainder deciles T4	781	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

<sup>2</sup>the top decile for TSH is actually the top 9-14% dependent on day of test % as the TSH kit only provided integer results

**SUPPLEMENTARY TABLE 8:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III Gross Motor subtest scores

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Gross Motor Score Day 7</b>						
Top decile TSH <sup>2</sup>	184	-0.2	-0.827	0.409	-0.6	0.3
Remainder deciles TSH	754	reference				
Bottom decile TBG	83	<0.1	0.092	0.927	-0.6	0.6
Remainder deciles TBG	855	reference				
Bottom decile T4/TBG ratio	88	<0.1	0.273	0.785	-0.5	0.7
Remainder deciles T4/TBG ratio	850	reference				
Bottom decile T4	93	<-0.1	-0.270	0.787	-0.7	0.5
Remainder deciles T4	853	reference				
<b>Gross Motor Score Day 14</b>						
Top decile TSH	182	-0.2	-0.959	0.338	-0.7	0.2
Remainder deciles TSH	769	reference				
Bottom decile TBG	86	0.3	1.010	0.313	-0.3	0.9
Remainder deciles TBG	865	reference				
Bottom decile T4/TBG ratio	91	-0.4	-1.382	0.167	-1.0	0.2
Remainder deciles T4/TBG ratio	860	reference				
Bottom decile T4	86	-0.7	-2.188	0.029	-1.3	<-0.1
Remainder deciles T4	868	reference				
<b>Gross Motor Score Day 28</b>						
Top decile TSH	131	<-0.1	-0.028	0.978	-0.5	0.5
Remainder deciles TSH	779	reference				
Bottom decile TBG	87	0.2	0.634	0.526	-0.4	0.8
Remainder deciles TBG	824	reference				
Bottom decile T4/TBG ratio	81	-0.3	-0.866	0.387	-0.9	0.3
Remainder deciles T4/TBG ratio	830	reference				
Bottom decile T4	78	-0.4	-1.237	0.216	-1.0	0.2
Remainder deciles T4	834	reference				
<b>Gross Motor Score 34 weeks'</b>						
Top decile TSH	269	0.1	0.539	0.590	-0.3	0.5
Remainder deciles TSH	593	reference				
Bottom decile TBG	87	-0.2	-0.587	0.557	-0.8	0.4
Remainder deciles TBG	775	reference				
Bottom decile T4/TBG ratio	74	-0.2	-0.496	0.620	-0.8	0.5
Remainder deciles T4/TBG ratio	788	reference				
Bottom decile T4	80	-0.3	-0.908	0.364	-0.9	0.3
Remainder deciles T4	782	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

<sup>2</sup>the top decile for TSH is actually the top 9-14% dependent on day of test as the TSH kit only provided integer results

**SUPPLEMENTARY TABLE 9:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III main domain scores

Bayley-III main domains	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Cognitive Score Day 7</b>						
Hypothyroid	6	-20.8	-3.316	0.001	-33.2	-8.5
Hyperthyrotropinaemic	12	2.5	0.519	0.604	-6.8	11.7
Hypothyroxinaemic	451	-2.0	-1.660	0.097	-4.3	0.4
Euthyroid	470	reference				
<b>Cognitive Score Day 14</b>						
Hypothyroid	11	1.1	0.222	0.824	-8.9	11.2
Hyperthyrotropinaemic	20	-0.7	-0.169	0.866	-8.2	6.9
Hypothyroxinaemic	281	-1.3	-0.986	0.324	-3.9	1.3
Euthyroid	640	reference				
<b>Cognitive Score Day 28</b>						
Hypothyroid	5	-2.9	-0.406	0.685	-16.6	11.0
Hyperthyrotropinaemic	13	-10.2	-2.352	0.019	-18.8	-1.7
Hypothyroxinaemic	154	-0.9	-0.647	0.518	-3.8	1.9
Euthyroid	739	reference				
<b>Cognitive Score 34 weeks'</b>						
Hypothyroid	2	3.6	0.315	0.753	-18.7	25.9
Hyperthyrotropinaemic	12	-6.9	-1.534	0.125	-15.7	1.9
Hypothyroxinaemic	84	-1.4	-0.733	0.464	-5.0	2.3
Euthyroid	765	reference				
<b>Motor Composite Score Day 7</b>						
Hypothyroid	6	-17.2	-2.828	0.005	-29.1	-5.3
Hyperthyrotropinaemic	12	3.0	0.650	0.516	-6.0	11.9
Hypothyroxinaemic	450	-2.0	-1.719	0.086	-4.3	0.3
Euthyroid	470	reference				
<b>Motor Composite Score Day 14</b>						
Hypothyroid	11	-1.8	-0.370	0.712	-11.6	7.9
Hyperthyrotropinaemic	20	-0.3	-0.070	0.944	-7.6	7.1
Hypothyroxinaemic	281	-1.5	-1.190	0.234	-4.1	1.0
Euthyroid	639	reference				
<b>Motor Composite Score Day 28</b>						
Hypothyroid	5	-6.0	-0.895	0.371	-19.3	7.2
Hyperthyrotropinaemic	13	-5.0	-1.184	0.237	-13.2	3.3
Hypothyroxinaemic	154	-2.5	-1.764	0.078	-5.2	0.3
Euthyroid	738	reference				
<b>Motor Composite Score 34 weeks'</b>						
Hypothyroid	2	-7.1	-0.644	0.520	-28.7	14.5
Hyperthyrotropinaemic	12	-2.9	-0.662	0.508	-11.4	5.7
Hypothyroxinaemic	84	-1.5	-0.826	0.409	-5.0	2.0
Euthyroid	764	reference				
<b>Language Composite Score DAY 7</b>						
Hypothyroid	6	-15.5	-2.181	0.029	-29.4	-1.6
Hyperthyrotropinaemic	12	-0.5	-0.094	0.925	-11.0	10.0
Hypothyroxinaemic	450	-1.3	-0.970	0.332	-4.0	1.3
Euthyroid	469	reference				
<b>Language Composite Score DAY 14</b>						
Hypothyroid	11	3.2	0.556	0.578	-8.1	14.5
Hyperthyrotropinaemic	20	0.2	0.054	0.957	-8.3	8.7
Hypothyroxinaemic	281	-1.8	-1.189	0.235	-4.7	1.2
Euthyroid	639	reference				
<b>Language Composite Score DAY 28</b>						
Hypothyroid	5	-5.6	-0.711	0.477	-21.1	9.9
Hyperthyrotropinaemic	13	-5.6	-1.136	0.256	-15.2	4.1
Hypothyroxinaemic	154	-0.6	-0.364	0.716	-3.8	2.6
Euthyroid	737	reference				
<b>Language Composite Score 34 weeks'</b>						
Hypothyroid	2	8.3	0.659	0.510	-16.4	33.0
Hyperthyrotropinaemic	12	-2.8	-0.577	0.577	-12.5	7.0
Hypothyroxinaemic	84	0.4	0.211	0.833	-3.6	4.4
Euthyroid	763	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

**SUPPLEMENTARY TABLE 10:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III language subtest scores

Bayley-III subtest scores	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Receptive Language Score DAY 7</b>						
Hypothyroid	6	-2.1	-1.614	0.107	-4.6	0.4
Hyperthyrotropinaemic	12	<0.1	0.008	0.994	-1.9	1.9
Hypothyroxinaemic	450	-0.3	-1.397	0.163	-0.8	0.1
Euthyroid	469	reference				
<b>Receptive Language Score DAY 14</b>						
Hypothyroid	11	0.4	0.424	0.672	-1.6	2.5
Hyperthyrotropinaemic	20	0.2	0.265	0.791	-1.3	1.7
Hypothyroxinaemic	281	-0.3	-1.158	0.247	-0.8	0.2
Euthyroid	639	reference				
<b>Receptive Language Score DAY 28</b>						
Hypothyroid	5	-1.5	-1.039	0.299	-4.3	1.3
Hyperthyrotropinaemic	13	-0.9	-0.969	0.333	-2.6	0.9
Hypothyroxinaemic	154	-0.3	-1.090	0.276	-0.9	0.3
Euthyroid	737	reference				
<b>Receptive Language Score 34 weeks'</b>						
Hypothyroid	2	1.5	0.656	0.512	-3.0	5.9
Hyperthyrotropinaemic	12	-0.8	-0.921	0.357	-2.6	0.9
Hypothyroxinaemic	84	-0.1	-0.204	0.839	-0.8	0.7
Euthyroid	763	reference				
<b>Expressive Language Score DAY 7</b>						
Hypothyroid	6	-3.2	-2.496	0.013	-5.8	-0.7
Hyperthyrotropinaemic	12	-0.2	-0.183	0.855	-2.1	1.7
Hypothyroxinaemic	449	-0.1	-0.515	0.607	-0.6	0.4
Euthyroid	469	reference				
<b>Expressive Language Score DAY 14</b>						
Hypothyroid	11	0.6	0.594	0.552	-1.4	2.7
Hyperthyrotropinaemic	20	-0.1	-0.168	0.867	-1.7	1.4
Hypothyroxinaemic	280	-0.3	-1.117	0.264	-0.9	0.2
Euthyroid	639	reference				
<b>Expressive Language Score DAY 28</b>						
Hypothyroid	5	-0.5	-0.317	0.752	-3.3	2.4
Hyperthyrotropinaemic	13	-1.0	-1.142	0.254	-2.8	0.7
Hypothyroxinaemic	154	<0.1	0.274	0.784	-0.5	0.7
Euthyroid	736	reference				
<b>Expressive Language Score 34 weeks'</b>						
Hypothyroid	2	1.2	0.508	0.612	-3.3	5.7
Hyperthyrotropinaemic	12	-0.1	-0.158	0.875	-1.9	1.6
Hypothyroxinaemic	84	0.2	0.490	0.624	-0.6	0.9
Euthyroid	762	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

**SUPPLEMENTARY TABLE 11:** Adjusted<sup>1</sup> linear regression models of thyroid function on postnatal day 7, 14, 28 and the equivalent of 34 weeks' gestation and the Bayley-III motor subtest scores

Bayley-III subtest scores	N	Effect estimate	T statistic	p value	95% confidence interval	
					Lower	higher
<b>Fine motor Score DAY 7</b>						
Hypothyroid	6	-3.4	-2.812	0.005	-5.7	-1.0
Hyperthyrotropinaemic	12	<0.1	0.093	0.926	-1.7	1.9
Hypothyroxinaemic	449	-0.4	-1.634	0.103	-0.8	<0.1
Euthyroid	470	reference				
<b>Fine motor Score DAY 14</b>						
Hypothyroid	11	0.3	0.271	0.787	-1.7	2.2
Hyperthyrotropinaemic	20	-0.7	-0.982	0.327	-2.2	0.7
Hypothyroxinaemic	281	-0.3	-1.182	0.238	-0.8	0.2
Euthyroid	638	reference				
<b>Fine motor Score DAY 28</b>						
Hypothyroid	5	-1.0	-0.764	0.445	-3.6	1.6
Hyperthyrotropinaemic	13	-1.9	-2.301	0.022	-3.5	-0.3
Hypothyroxinaemic	154	-0.3	-1.085	0.278	-0.9	0.2
Euthyroid	738	reference				
<b>Fine motor Score DAY 34 weeks'</b>						
Hypothyroid	2	-1.7	-0.787	0.432	-5.9	2.5
Hyperthyrotropinaemic	12	-0.6	-0.698	0.486	-2.3	1.1
Hypothyroxinaemic	84	-0.3	-0.833	0.405	-1.0	0.4
Euthyroid	763	reference				
<b>Gross motor Score DAY 7</b>						
Hypothyroid	6	-2.3	-2.161	0.031	-4.5	-0.2
Hyperthyrotropinaemic	12	1.0	1.228	0.220	-0.6	2.6
Hypothyroxinaemic	451	-0.3	-1.404	0.161	-0.7	0.1
Euthyroid	469	reference				
<b>Gross motor Score DAY 14</b>						
Hypothyroid	11	-0.9	-0.993	0.321	-2.6	0.9
Hyperthyrotropinaemic	20	0.6	0.960	0.337	-0.7	2.0
Hypothyroxinaemic	281	-0.3	-1.140	0.255	-0.7	0.2
Euthyroid	639	reference				
<b>Gross motor Score DAY 28</b>						
Hypothyroid	5	-0.9	-0.777	0.437	-3.3	1.4
Hyperthyrotropinaemic	13	0.3	0.356	0.722	-1.2	1.7
Hypothyroxinaemic	153	-0.5	-2.001	0.046	-1.0	<-0.1
Euthyroid	739	reference				
<b>Gross motor Score 34 weeks'</b>						
Hypothyroid	2	-0.6	-0.311	0.756	-4.5	3.3
Hyperthyrotropinaemic	12	-0.3	-0.393	0.695	-1.9	1.2
Hypothyroxinaemic	84	-0.2	-0.667	0.505	-0.9	0.4
Euthyroid	764	reference				

<sup>1</sup>adjusted for gender, gestational age, level of nursing care required on day of blood sampling, whether or not in receipt of iodine supplement, and whether or not treated with L-Thyroxine during the neonatal period or at 2 years of age, assessor, hospital of birth and T4:TBG ratio on day 7,14,28 or 34 weeks' as appropriate.

## SUPPLEMENTARY FIGURE



